SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

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I. GENERAL INFORMATION

Device Generic Name:	Free Prostate Specific Antigen (free PSA)
Device Trade Name:	AxSYM® Free PSA
Applicant's Name and Address:	Abbott Laboratories 200 Abbott Park Road Abbott Park, Illinois 60064-3537
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P980007
Date of Notice of Approval to Applicant:	February 4, 2004

II. INDICATIONS FOR USE

The AxSYM® Free PSA assay is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative measurement of free prostate specific antigen (PSA) in human serum. The AxSYM Free PSA assay is intended to be used in conjunction with the AxSYM Total PSA assay in men aged 50 years or older with total PSA values between 4 and 10 ng/mL and non-suspicious DRE, to determine the % free PSA value. The AxSYM % free PSA value can be used as an aid in discriminating between prostate cancer and benign disease.

III. CONTRAINDICATIONS

None known

IV. WARNINGS AND PRECAUTIONS

Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits which employ mouse monoclonal antibodies. These specimens should not be assayed with the AxSYM® Free PSA assay. Refer to the **LIMITATIONS OF THE PROCEDURE** section in the assay package insert.

Other warnings and precautions can be found in the labeling.

V. DEVICE DESCRIPTION

Device Description

The AxSYM Free PSA assay is based on microparticle enzyme immunoassay technology, and requires the use of the AxSYM System. The analyzer performs all sample and reagent transfers, incubations, and data processing and produces a printed report. Sample and all AxSYM Free PSA reagents required for one test are pipetted by the Sampling Probe into various wells of a reaction vessel (RV) in the Sampling Center. The RV is transferred into the Processing Center, where further pipetting steps are performed.

The sample, Anti-PSA Coated Microparticles, and Assay Diluent are incubated together in one well of the reaction vessel. The PSA in the specimen binds to the Anti-PSA Coated Microparticles forming an antibody-antigen complex. An aliquot of the reaction mixture is transferred to a cell containing a glass fiber matrix where the microparticles bind irreversibly to the glass fiber matrix and are washed to remove unbound particles. Alkaline Phosphatase-conjugated Anti-Free PSA antibody mixed with the sample binds to the antibody-antigen complex and the matrix cell is washed to remove unbound materials. The substrate is added and its fluorescent product is measured by the instrument optical assembly. The concentration of free PSA in the sample is determined using a previously generated calibration curve.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Alternative practices and procedures for aiding in the detection of prostate cancer include physical examination using digital rectal examination (DRE) and diagnostic imaging by transrectal ultrasound (TRUS). Confirmation of prostate cancer is determined by biopsy. Other FDA approved devices for measuring serum total PSA are available to aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years and older.

VII. MARKETING HISTORY

This product (AxSYM Free PSA, List Number [LN] 3C20) has been marketed outside the United States since April 1997. The device has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential Effects

Although the AxSYM % free PSA value is not diagnostic for prostate cancer, the presence of low %free PSA may lead to failure to detect prostate cancer on first biopsy sampling. If the AxSYM %

free PSA value is inconsistent with clinical evidence, additional testing is suggested to confirm the result. Confirmation of prostate cancer can only be determined by prostatic biopsy.

The application of the % free PSA value in the diagnostic gray zone of 4 to 10 ng/mL PSA will fail to detect a percentage of cancers that would have been detected, if all patients with a PSA above 4 ng/mL were routinely biopsied.

An error in the assay which would produce a falsely elevated AxSYM % free PSA value, could delay recognition of the presence of prostate cancer by the physician. In this case, the patient could be adversely affected by a delay in the initiation of therapy. A falsely low AxSYM % free PSA value could lead to an unnecessary biopsy.

IX. SUMMARY OF PRECLINICAL STUDIES

Laboratory Studies

Recovery - A study assessed the recovery of free PSA by adding known levels of free PSA to normal human serum. The recovery in serum ranged from 93 to 102%, indicating accurate quantitation of the free PSA in human serum.

Specificity - Interfering Substances - Two studies evaluated the potential sources of interference associated with endogenous substances present in clinical specimens.

The first study was performed by addition of potential interfering substances and free PSA to normal human serum. The interference in serum free PSA determinations was less than 10%, indicating accurate quantitation in the presence of potentially interfering substances.

The second study was performed by addition of free PSA to patient samples containing high levels of potentially interfering substances. The recoveries of free PSA ranged from 90 to 110%, indicating accurate quantitation of free PSA in the presence of potentially interfering substances.

Specificity - Chemotherapeutic Agents - The addition of commonly used chemotherapeutic agents to normal human serum was use to evaluate interference with the AxSYM Free PSA assay by these agents. The recoveries of free PSA ranged from 90 to 110%, indicating that the tested chemotherapeutic agents did not interfere with quantitation in the AxSYM Free PSA assay.

On-board Reagent Stability - Three AxSYM Free PSA reagent lots were stored for 336 hours onboard the AxSYM instrument. Free PSA controls assessed assay performance of stored reagent lots compared with reagent packs stored at 2 to 8°C continuously. Free PSA control results were within specification for 336 hours, indicating that the AxSYM Free PSA reagents are stable while onboard the AxSYM instrument. Recalibration may be required to obtain maximum on-board reagent stability.

Sample Carryover - Sample carryover within the AxSYM Free PSA assay was tested using a sample containing a high level of free PSA followed by negative samples. Carryover was 2.5 parts

per million (PPM) or less. The PPM level is equivalent to 0.042 ng/mL caryover from a sample of 17,115 ng/mL. This result indicates no significant carryover within the AxSYM Free PSA assay.

Sample carryover into the AxSYM Free PSA assay from other AxSYM assays was tested using a sample containing a high concentration of free PSA serially in different AxSYM assays, followed by the AxSYM Free PSA assay containing a negative sample. Each AxSYM assay serially diluted the sample containing the free PSA. Carryover was 0.49 PPM or less, indicating no significant carryover into the AxSYM Free PSA assay from other AxSYM assays.

High Dose Hook Effect - A sample containing a high concentration (68,000 ng/mL) of free PSA was logarithmically diluted and was tested in the assay to assess high dose hook effect. Samples and dilutions with free PSA concentrations above the dynamic range of the assay (10 ng/mL) gave the appropriate error flags demonstrating that there is no high dose 'hook' effect in the AxSYM Free PSA assay.

Cross Reactivity with PSA-ACT - Cross reactivity with PSA-ACT (PSA-alpha-1-antichymotrypsin) was tested in the free PSA assay using a sample containing 106.43 ng/mL of purified PSA-ACT. The percent cross reactivity was less than 1%, indicating that samples containing up to 106 ng/mL of PSA-ACT do not cross react in the AxSYM Free PSA assay.

2-Point Master Calibration Validation (2-Point Versus 6-Point) - A validation study was performed to demonstrate equivalency between 2-point master calibration to 6-point standard calibration. Assay values of 895 specimens were determined using both 2-point master calibration and 6-point standard calibration. A linear regression analysis of these values assessed the agreement between 2-point and 6-point values. The correlation coefficient from linear regression analysis (range: 0 to 10 ng/mL) was 0.9997 with a slope of 1.0049 and a y-intercept of 0.0011, indicating equivalent values from 2-point master calibrations and 6-point standard calibrations.

Reagent Stability - Stability was evaluated to determine the shelf-life of the AxSYM Free PSA reagents, Free PSA Calibrators and Controls. The results support a minimum of 11 months stability for the AxSYM Free PSA reagents, Free PSA Calibrators and Controls when stored at 2 to 8°C.

Sample Collection - Samples from serum and serum separator tubes were evaluated to demonstrate that no interference occurs in the AxSYM Free PSA assay when using serum separator tubes. Percent recovery from the serum separator tubes was 91-107%, indicating that no significant interference occurs in the AxSYM Free PSA assay from serum separator tubes.

Reagent Lot to Lot Performance - Lot to lot performance of the AxSYM Free PSA assay was assessed using a control and panel of human serum samples with three reagent master lots. The results indicated similar values across 3 lots of AxSYM Free PSA reagents.

Precision - Two precision studies (5 day and 20 day) determined the within run, between run, between day, and between lab, and total precision of the AxSYM Free PSA assay. In each study six samples were evaluated: three free PSA controls and three pools of normal human serum

having different added concentrations of free PSA. The samples were tested in duplicate, in two runs per day (separated by a minimum of two hours) for each of either 5 or 20 days. The following indicate the range of %CV for each precision study:

Precision study	**Range of %CV**				
	Within run	Between run	Between day	Between lot	total
5 day	4.81 to 6.13	0.00 to 1.26	0.00 to 1.02	0.00 to 1.44	4.91 to 6.27
	Within run	Between run	Between day	Between lab	total
20 day	3.22 to 3.68	1.94 to 2.83	2.45 to 3.77	3.16 to 4.71	5.83 to 7.44

Analytical Sensitivity - The lowest measurable concentration of free PSA statistically distinguishable from the 0 ng/mL free PSA calibrator in the AxSYM Free PSA assay was assessed. Two assays, each containing 10 replicates of the Free PSA Calibrator A (0 ng/mL), were performed for each of three lots of AxSYM Free PSA reagents at four outside sites. Three similar assays were performed for each lot at Abbott Laboratories. The lowest measurable concentration (analytical sensitivity) of free PSA was calculated by determining the free PSA mean ng /mL value corresponding to the fluorescence signal at two standard deviations above the mean of the Free PSA Calibrator A. The data support a sensitivity of less than 0.02 ng/mL.

Dilution Linearity - Dilution Linearity studies were performed to demonstrate that the calculated concentration of free PSA for specimens requiring dilution would not be influenced significantly by dilution. For each of 16 serum specimens with elevated free PSA values and for three serum specimens with free PSA values greater than 10 ng/mL, a minimum of four serial dilutions were prepared using the Free and Total PSA Specimen Diluent.

Linear regression analysis of the observed free PSA concentration (ng/mL) as a function of dilution (1/dilution factor) was performed and yielded correlation coefficients of greater than or equal to 0.996 with 19 samples. The mean and %CV of the free PSA values for each specimen were calculated and yielded mean %CVs of 3.36%, ranging from 1.79 to 6.05%. The percent recovery for each dilution and the mean percent recovery for each specimen was calculated and ranged from 91.3 to 105.1%. The average percent recoveries for the AxSYM Free PSA assay Dilution studies indicate that free PSA concentration, when corrected for dilution, is not significantly affected by sample dilution.

Automated (1:10) Dilutions - The Automated Dilution study was performed to validate the AxSYM Free PSA autodilution protocol. Fifty-three specimens with AxSYM Free PSA values greater than the highest calibrator (10 ng/mL) were tested at five outside sites and at Abbott Laboratories using the 1:10 autodilution protocol. Diluted values from the autodilution procedure were within the assay range (<10 ng/mL) and above the Free PSA Calibrator B (0.2 ng/mL). For comparison, the specimens were manually diluted (1:10) and assayed in the AxSYM Free PSA assay. Linear regression analysis of the automated dilutions compared to manual dilution yielded a correlation coefficient of 0.991, slope of the best fit line of 1.03 (95% confidence interval 0.99 to 1.06), and y-intercept of 0.76 (95% confidence interval -0.53 to 2.05). The automated (1:10)

dilution protocol provides values that are clinically equivalent to values obtained from a manual dilution.

Single replicate vs duplicate values within a single run - The precision of a single replicate within a single run of the AxSYM Free PSA assay was compared to the precision using duplicates. A total of 232 clinical specimens covering the range of the standard curve were run at Abbott Laboratories in duplicate in the AxSYM Free PSA assay. A linear regression analysis compared the results of the second replicate to those of the first replicate. The analysis (second replicate versus first replicate) yielded a correlation coefficient of 0.999, slope of the best fit line of 1.00, and y- intercept of 0.10. The analysis indicates that each of the duplicate values in the AxSYM Free PSA assay are equivalent, so that single replicate values may be substituted for duplicate values.

Sample Stability - A study evaluated the stability of free PSA in serum specimens stored at 2 to 8°C and at room temperature, and the effect of multiple (three) freeze- thaw cycles.

The results show that serum samples can be stored for one day at 2 to 8°C with less than a 10% decrease in free PSA values (mean = 94.8%) and that samples stored at room temperature are slightly less stable than at 2 to 8°C storage. Multiple freeze-thaw cycle results showed no significant effect on free PSA values.

X. SUMMARY OF CLINICAL STUDIES

Clinical studies evaluated the range of free PSA values in apparently healthy normal individuals and the distribution of free PSA values in healthy individuals and individuals with malignant and non-malignant diseases. Studies also evaluated the clinical utility of the % free PSA value as an aid in discriminating prostate cancer from benign prostate diseases in men undergoing evaluation for prostate abnormalities.

Determination of Specimen Values for Apparently Health Subjects

Serum free PSA values from 999 males without clinical evidence of prostate cancer were determined in the AxSYM Free PSA assay. Two hundred and fifty males were less than 50 years of age and 749 were $\geq$ 50 years of age. Two groups of subjects were included:

- Subjects with a negative PSA value (< 4 ng/mL) and negative digital rectal exam (DRE)
- Subjects with a positive DRE and/or a positive PSA value ($\geq$ 4 ng/mL) but a negative prostatic biopsy.

AxSYM Free PSA specimen values in this study ranged from 0.001 to 5.086 ng/mL. Ninety-five percent of the free PSA values were 0.934 ng/mL or less.

Distribution of Specimen Values

The distributions of AxSYM Free PSA values and % free PSA values were determined in a retrospective study using surplus specimens from healthy subjects and subjects with malignant and nonmalignant diseases. The study was performed at Abbott Laboratories and five additional

laboratories across the United States. A clinical history was obtained for each subject included in the study.

AxSYM Free PSA values were determined from 2,453 subjects:

- 999 healthy males
- 246 healthy females
- 368 subjects with benign prostatic hyperplasia (BPH)
- 191 subjects with other nonmalignant conditions
- 151 subjects with genitourinary cancer
- 498 subjects with prostate cancer.

For the healthy males, the AxSYM Free PSA values ranged from 0.001 to 5.086 ng/mL with 95.1% of the values falling in the 0.00 to 0.934 ng/mL range. For subjects with BPH, the AxSYM Free PSA values ranged from 0.00 to 127.04 ng/mL, with 26.4% falling above 0.934 ng/mL. For subjects with prostatitis, the AxSYM Free PSA values ranged from 0.003 to 8.68 ng/mL, with 22.9% falling above 0.934 ng/mL. For subjects with prostate cancer, the AxSYM Free PSA values ranged from 0.00 to 818.50 ng/mL, with 40.0% falling above 0.934 ng/mL.

The incidence of elevated free PSA values (greater than 0.934 ng/mL) is increased in subjects with BPH or prostatitis and especially in those with prostate cancer. For subjects with prostate cancer, the incidence of elevated free PSA values increases with disease stage. These increases are consistent with the previously known increases in total PSA values for these diseases.

Percent free PSA values were determined for a subset (n=621) of the 2,453 subjects whose total PSA values using the AxSYM Total PSA assay were between 2 and 20 ng/ml, including healthy males, subjects with BPH, and subjects with prostate cancer.

The % free PSA values were divided into five groups: $\leq$ 10%, > 10-15%, > 15-20%, > 20-26% and > 26%. Approximate percentages of subjects in each %free PSA range are illustrated in the following:

Percentage of subjects in the following ranges of %free PSA where Total PSA is 2-20 ng/ml

Subject	N	<10%	10-15%	15-20%	20-26%	>26%
Normal	172	10%	17%	23%	22%	28%
BPH	176	12%	16%	23%	17%	32%
cancer	275	45%	22%	16%	8%	9%

Subjects with prostate cancer had a lower % free PSA value compared to healthy subjects and subjects with BPH. Therefore, this data suggests that the use of % free PSA values improves the discrimination between BPH and prostate cancer in men with intermediate levels of total PSA.

Utility Study

The objective of this study was to confirm the hypothesis that the AxSYM % free PSA value has the potential to reduce the number of biopsies, when used as an aid in disriminating prostate cancer from benign prostate disease in men undergoing evaluation for prostate abnormality.

A prospective clinical study enrolled 588 eliglible subjects from 9 clinical sites across North America. Subjects were enrolled if they had PSA values between 4 and 20 ng/mL (as determined by the laboratory test of record), and/or a positive DRE, and were 50 years of age or older. All subjects were biopsied to confirm or rule out prostate cancer. Enrollment data included subject identification, collection of demographic and medical history, PSA value, result of DRE, and clinical reason for biopsy. A serum sample, drawn prior to biopsy and stored frozen, was retested using the AxSYM Total PSA and AxSYM Free PSA assays. Neither of these assays were used to decide treatment.

For 588 biopsied subjects, 371 (63.1%) were biopsy negative and 217 (36.9%) were biopsy positive.

Patient age ranged from 50 to 87 years, with a mean age of 66 years for all eligible patients. Age was not a significant variable across biopsy results (Wilcoxon rank-sum test: p=0.934). A chi-square test compared the race categories of black (n=49) and non-black (n=386) between biopsy positive and biopsy negative groups. No significant difference was found (p=0.127).

Among the 217 biopsy positive subjects, 123 (56.7%) had negative DRE results and 94 (43.3%) had positive DRE results. Of the 371 biopsy negative subjects, 269 (72.5%) had negative DRE results and 102 (27.5%) had positive DRE results. Using a chi-square test, the percentage of DRE positive subjects in the biopsy positive group was significantly higher than the biopsy negative group (p=0.001).

A Wilcoxon rank-sum test compared median values for total PSA and % free PSA values between the biopsy positive and biopsy negative subject groups. The median total PSA value (5.8) was higher (p=0.0017) for biopsy positive subjects than for biopsy negative subjects (5.3). The median % free PSA value (13.4) was lower (p=0.0001) for biopsy positive subjects than for biopsy negative subjects (21.9).

A linear regression analysis of % free PSA and total PSA was performed to test for an association between the values. The correlation coefficient (0.241) was significant ($p < 0.0001$) and was a negative correlation.

Pooling of data across sites

The cancer rate at each site ranged from 0% to approximately 75%. The mean rate for all sites was 38.4%. The frequency of cancers at each site was significantly different ($p < 0.0001$, using a Chi square test for homogeneity).

Analysis of variance of the total PSA at each site indicated significant differences ($p < 0.0001$, F-value 9.197 for 8 and 603 degrees of freedom). The mean total PSA ranged from 4.0 ng/ml to 10.2 ng/ml. The overall mean total PSA was 6.2 ng/ml. Similar analysis of the mean age at each site indicated significant differences ($p < 0.0001$, F-value 12.048 for 8 and 603 degrees of freedom). The mean age ranged from 61.7 to 69.5 years (overall mean 66.3 years). Analysis of the mean % free PSA at each site additionally indicated significant differences ($p < 0.0001$, F-value 5.189 for 8 and 603 degrees of freedom). The mean % free PSA at each site ranged from 15.6% to 26.5% (overall mean 20.6%).

The differences in cancer rate, age, mean total PSA, and mean % free PSA at each site imply differences in patient populations at each site. It is unclear why these characteristics are different.

It is possible that diagnostic test performance could be similar at each site despite differences in patient characteristics. Two diagnostic tests, total PSA and DRE, were chosen because they are used to select patients for follow-up. Odds ratio estimation for cancer and analysis of probability of homogeneity of odds ratios across all sites were performed on two subject groups: elevated total PSA (> 4 ng/mL), and abnormal DRE. The odds ratios for cancer given an elevated total PSA ranged from 0.17 to 7.6 (overall odds ratio 1.63, 95% confidence interval of ratio 1.015 to 2.623). The probabilty of homogeneous odds ratios was not significant ($p > 0.05$). The odds ratio for cancer given an abnormal DRE ranged from 0.79 to 121 (overall odds 2.495, 95% confidence interval 1.764 to 3.529). The probability of homogeneous odds ratios was not significant ($p = 0.081$). The analysis supports a conclusion of similar diagnostic performance at each site for each diagnostic test.

To assess the homogeneity of test performance for the %free PSA test, the odds ratios for cancer given a % free PSA <25% were calculated for each site. The mean odds ratio for all sites was 3.84 (95% confidence interval 2.72 to 5.41), where odds ratios ranged from 0.671 to 12.667. The probability of homogeneous odds ratios was not significant ($p > 0.05$). This analysis supports a conclusion of similar performance of these tests to diagnose cancer at each site. Since all three analyses indicated no significant differences in test performance at each site, there is a rationale for pooling the data from each site for final analysis.

Determination of Optimal Total PSA Range

An optimal range of total PSA values was determined which provides the maximum area under the receiver operating characteristic (ROC) curve for the % free PSA value. A ROC curve was calculated for total PSA and % free PSA using all 588 subjects. The result of comparing areas under the curve indicated that the area for % free PSA is significantly higher than the area for total PSA ($p<0.0001$). The specificity of the % free PSA values was compared to the specificity of the total PSA test using the McNemar test, when the sensitivity of both tests is maintained at the sensitivity value for total PSA at 4.0 ng/mL. Using the standard cutoff of 4.0 ng/mL, the AxSYM Total PSA assay had a sensitivity of 83% and a specificity of 31.5%. The % free PSA value with a cutpoint of 22.4% gave a sensitivity of 83.4% and a specificity of 48%. The % free PSA value demonstrated a statistically significant increase in specificity ($p\leq0.001$) over the total PSA value.

The area under the ROC curves for total PSA and for % free PSA was calculated for 36 subgroups of the 588 subjects with a total PSA value within a selected lower limit and upper limit. The selections for lower limits were 0, 2.0, 2.5, 3.0, 3.5, 4.0 ng/mL: the selections for upper limits were 20.0, 15.0, 12.0, 10.0, 8.0, and 6.0 ng/mL.

The AUC for total PSA ranged from 0.453 to 0.598 across the ranges of total PSA, demonstrating that total PSA has little utility in differentiating between cancer and non-cancer within these ranges. The AUC for % free PSA were greater than those for total PSA across all PSA subgroups. The AUC for % free PSA ranged from 0.738 to 0.792 indicating less variation in the clinical performance of % free PSA across these total PSA ranges. The difference between AUCs for % free PSA and total PSA was greatest when the lower limit was 4.0 ng/mL and the upper limit was 10 ng/mL (AUC for total PSA= 0.453, AUC for % free PSA= 0.773).

Percent (%) Free PSA Cutoffs

Cutoffs for % free PSA were identified that would yield a sensitivity of at least 90% or 95%, and a specificity of at least 90% or 95% for subjects with a non-suspicious DRE result and a total PSA range of 4 to10 ng/mL. The total and free PSA values were determined using the AxSYM Total PSA and AxSYM Free PSA assays for 271 subjects (181 non-cancer; 90 cancer) with total PSA values between 4 and 10 ng/mL and DRE non-suspicious for cancer. The cancer prevalence rate for this group was 33%.

The following table shows the % free PSA cutoffs at or above 90% and 95% specificity and sensitivity.

Percent Free PSA Cutoffs at or Above 90% and 95% Sensitivity and Specificity

% Free PSA	Sensitivity (%)	95% CI	Specificity (%)	95% CI
9.7	24.4	(16.0,34.6)	95	(90.8,97.7)
10.9	32.2	(22.8,42.9)	90.1	(84.7,94.0)
23.6	90	(81.9,95.3)	40.3	(33.1,47.9)
26.4	96.7	(90.6,99.3)	28.2	(21.8,35.3)

Using the same test results, the % free PSA levels were divided into five groups. The range for these % free PSA groups are: $\leq$ 10, >10-15, >15-20, > 20-26 and > 26. The distribution of % free PSA values are shown in the table below. The incidence of prostate cancer was higher in the subjects with lower % free PSA values .

Distribution of AxSYM % free PSA Values for Specimens with AxSYM Total PSA Between 4 and 10 ng/mL

		% Free PSA Ranges				
	Number of Subjects	≤10	>10-15	>15-20	>20-26	>26
Biopsy Negative	181	6.1%	16.0%	24.9%	24.9%	28.2%
Biopsy Positive	90	30.0%	28.9%	22.2%	13.3%	5.6%

Probability of Prostate Cancer

The probabilities of prostate cancer given specific ranges for % free PSA were calculated based on a logistic regression model using subjects with total PSA values between 4 and 10 ng/mL and DRE non-suspicious for cancer and a disease prevalence rate of 33%. The binary dependent variable was the biopsy result (cancer or non-cancer) and the independent variable was the category of % free PSA. Each % free PSA result was placed into one of the five categories: $\leq$ 10, > 10-15, > 15-20, > 20-26 and > 26.

The chi-square test of the -2 Log Likelihood Statistic for the model shows that there is a significant relationship between % free PSA categories and biopsy result (<0.0001). The Hosmer-Lemeshow

goodness-of-fit test was not significant (p=0.8706) indicating the appropriateness of the model for these data. The probability of cancer given different categories of % free PSA is shown in the following table.

Probability of Prostate Cancer at a Prevalence Rate of 33% For Subjects with AxSYM Total PSA between 4 and 10 ng/mL and DRE Non-suspicious for Cancer

% Free PSA Ranges				
≤10	>10-15	>15-20	>20-26	>26
67.9% *(56.4,77.6)	50.0% (41.9,58.2)	32.1% (26.3,38.6)	18.3% (13.0,25.0)	9.6% (5.5,16.0)

*(95% CI)

Prostate cancer probabilities associated with % free PSA values are dependent on the disease prevalence within a study population.[25] The table below shows the distribution of cancer probabilities for the five ranges of % free PSA using the same study population adjusted for different rates of disease prevalence.

Probability of Prostate Cancer by Disease Prevalence For Subjects with AxSYM Total PSA Between 4 and 10 ng/mL and DRE Non-suspicious for Cancer.

Prevalence	% Free PSA Ranges				
	≤ 10	> 10- 15	> 15 - 20	>20 - 26	> 26
20	51.6	33.5	19.2	10.1	5.1
25 *	58.7	40.2	24.1	13	6.6
30	64.6	46.3	29	16.2	8.4
35	69.6	52	33.9	19.5	10.3
40	74	57.3	38.8	23.1	12.4
45	77.7	62.2	43.8	26.9	14.8

* See data in Catalona WJ, Partin AW, Slawin KM, et al. Use of the Percentage of Free Prostate-Specific Antigen to Enhance Differentiation of Prostate Cancer From Benign Prostatic Disease. *JAMA*; 1998; 279:1542-1547.

The probability of cancer increased with decreasing % free PSA values. An ROC curve compared the performance of the probability model with that of total PSA. The AUC for the probability model was 0.7465 versus 0.4715 for total PSA (p<0.0001). The ROC curve comparing the performance of the probability model with % free PSA showed that the probability model and the % free PSA had similar (p=0.0868) areas under the curve (0.7465 and 0.7587 respectively).

Clinical Investigations - Study Conclusions

Clinical Utility

The primary objective of this study was to compare the specificity of % free PSA to the specificity of the total PSA test in men with negative biopsies, when the sensitivity of both tests are maintained at the sensitivity of total PSA using the current cutoff level (4.0 ng/mL). At comparable sensitivities of 83 and 83.4%, the AxSYM Total PSA assay and % free PSA assay had specificities of 31.5% and 48%, respectively. The 16.5% increase in specificity for % free PSA was statistically significant ($p \leq 0.001$).

The results of this study demonstrated that % free PSA contributed to the prediction of cancer and spared a proportion of men without cancer from an unecessary biopsy. These data support the clinical utility of the AxSYM Free PSA assay when used in conjunction with the AxSYM Total PSA assay to determine the % free PSA value in men aged 50 years or older with total PSA values between 4 and 10 ng/mL and non-suspicious DRE. The AxSYM % free PSA value can be used as an aid in discriminating between prostate cancer and benign disease.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Safety

The test presents no more safety hazard than other tests where blood is removed from subjects.

Effectiveness

Clinical data demonstrate that AxSYM Free PSA is effective for the quantitative measurement of free PSA in human serum and when used in conjunction with the AxSYM Total PSA assay in men aged 50 years or older with total PSA values between 4 and 10 ng/mL and non-suspicious DRE. The device is used to determine the % free PSA value to aid in discriminating between prostate cancer and benign disease.

Risk Benefit Analysis

The use of a % free PSA value of 26% could eliminate an unnecessary biopsy in 29% of subjects with benign disease, while identifying approximately 95% of the subjects with prostate cancer.

It is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used in accordance with the directions for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on February 4, 2004.
The applicant's manufacturing facility was found to be in compliance with the Quality Systems Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See the Approval Order.